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(21) International Application Number: PCT/SE99/02197 (22) International Filing Date: 25 November 1999 (25.11.99) (30) Priority Data: 9804064-5 25 November 1998 (25.11.98) SE (71) Applicant (for all designated States except US): A+ SCIENCE INVEST AB [SE/SE]; P.O. Box 3096, S-400 10 Göteborg (SE). (72) Inventor; and (75) Inventor/Applicant (for US only): ERIKSSON, Peter [SE/SE]; Dr. Saléns Gata 10, S-413 22 Göteborg (SE). (74) Agent: AWAPATENT AB; P.O. Box 11394, S-404 28 Göteborg (SE).	(81) Designated States: AE, AL, AM, AT, AT (Utility model), AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, CZ (Utility model), DE, DE (Utility model), DK, DK (Utility model), DM, EE, EE (Utility model), ES, FI, FI (Utility model), GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SK (Utility model), SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i> (88) Date of publication of the international search report: 17 August 2000 (17.08.00)	
(54) Title: MEDICINAL PRODUCT AND METHOD FOR TREATMENT OF CONDITIONS AFFECTING NEURAL STEM CELLS OR PROGENITOR CELLS		
(57) Abstract Use of a substance that upon administration will lead to increased concentrations of growth hormone, such as growth hormone, a functionally equivalent analogue thereof or a substance that will increase the release of endogenous growth hormone, for the production of a medicinal product for treatment of abnormal conditions affecting neural stem cells, progenitor cells and/or cells derived from neural stem cells or progenitor cells, especially conditions affecting the oligodendroglia, astroglia, and/or neuronal cells. In vitro and in vivo methods for inducing lineage determination, propagating and/or inducing or maintaining the genesis of neurons, oligodendrocytes, astroglial cells from progenitor cells, stem cells and/or cells derived from said cells by administering to the cells a substance that increases the concentration of growth hormone. Also a method of reducing the genesis of oligodendrocytes, neurons, astroglial cells from progenitor cells or stem cells, wherein a pharmaceutically effective amount of a substance that will lead to a decreased concentration of growth hormone or a functionally equivalent analogue thereof is administered to said patient.		

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 99/02197

A. CLASSIFICATION OF SUBJECT MATTER

IPC7: A61K 38/27, C12N 5/06

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC7: A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0324037 A1 (AROONSAKUL, CHAOVANE), 19 July 1989 (19.07.89), claim 7	1-12,17-27
A	--	16,28-29
X	WO 9422469 A1 (OHIO UNIVERSITY), 13 October 1994 (13.10.94), claim 1 and the abstract	1-12,17-27
A	--	16,28-29
X	WO 9410292 A1 (NEUROSPHERES LTD.), 11 May 1994 (11.05.94), page 14, lines 25-26	16,28-29
A	--	1-12,17-27

☒ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents:

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"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

8 May 2000

Date of mailing of the international search report

18-05-2000

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 99/02197

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 8805052 A1 (THE ADMINISTRATORS OF THE TULANE EDUCATIONAL FUND), 14 July 1988 (14.07.88), page 3, line 19 - line 20; page 6, line 17 --	13-14
X	GB 2198134 A (SANDOZ LTD.), 8 June 1988 (08.06.88), page 24, line 1 - line 3; page 26, line 1 - line 3; page 26, line 14 - line 17 --	13-14
X	WO 9012811 A1 (THE ADMINISTRATORS OF THE TULANE EDUCATIONAL FUND), 1 November 1990 (01.11.90), page 15, line 16, claims 1,10 --	13-14
A	WO 9615226 A1 (NEUROSFERES HOLDINGS LTD.), 23 May 1996 (23.05.96), page 7, line 17 - page 8, line 2; page 8, line 15 - line 19 --	13-15,30-34
A	WO 9204442 A1 (THE REGENTS OF THE UNIVERSITY OF CALIFORNIA), 19 March 1992 (19.03.92) --	13-15,30-34
A	Dialog Information Services, File 155, Medline, Dialog accession no. 05805167, Medline accession no. 89262444, Morisawa K et al: "Factors contributing to cerebral hypomyelination in the growth hormone-deficient little mouse", Neurochem Res (UNITED STATES) Feb 1989, 14 (2) p 173-7 --	13-15,30-34
A	Progress in Neurobiology, Volume 56, 1998, Christine C. Stichel et al, "Experimental strategies to promote axonal regeneration after traumatic central nervous system injury" page 119 - page 148 -- -----	13-15,30-34

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 99/02197**Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)**

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: **17-34**
because they relate to subject matter not required to be searched by this Authority, namely:
Claims 17-34 relate to methods of treatment of the human or animal body by therapy (Rule 39.1.(iv)). Nevertheless, a search has been executed and based on the alleged effects of the compounds.
2. ☒ Claims Nos.: **1, 13, 17 and 30**
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
see next sheet
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).:

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see next sheet

1. ☒ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

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Box I.2

The wording "...a substance... will lead to an increased/decreased concentration of growth hormone or a functionally equivalent analogue thereof..." is a functional determination that is considered to cover many different substances in addition to those mentioned in the application. Therefore, the international search has been incomplete.

Box II

As is stated in Annex B to Administrative instructions under the PCT, in force July 1, 1992 (PCT GAZETTE 1992, June 25, pages 7062-9, see page 7063 and example 5) unity of invention exists only when there is a technical relationship among the claimed inventions involving one or more of the same or corresponding "special technical features" - i.e. features that define a contribution which each of the inventions makes over the prior art. (c.f. PCT Rule 13.2)

A search for this "special technical feature" mentioned in PCT Rule 13.2 among the independent claims did not reveal such a unifying, novel technical feature. Accordingly, the following inventions were found:

Invention A, claims 1-12 and 16-29, concerns the use of a substance that upon administration to a patient will lead to an increased concentration of growth hormone for the production of a medicinal product for treatment of an abnormal condition affecting neural stem cells, progenitor cells and/or cells derived from stem cells or progenitor cells.

Invention B, claims 13-15 and 30-34, concerns the use of a substance that upon administration to a patient will lead to a decreased concentration of growth hormone for the production of a medicinal product for treatment of an abnormal condition affecting the central nervous system, e.g. an abnormal condition caused by axonal damage.

INTERNATIONAL SEARCH REPORT
Information on patent family members

02/12/99

International application No.

PCT/SE 99/02197

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INTERNATIONAL SEARCH REPORT
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02/12/99

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INTERNATIONAL SEARCH REPORT
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International application No.

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CLAIMS

1. Use of a substance that upon administration to a patient will lead to an increased concentration of growth hormone or a functionally equivalent analogue thereof for the production of a medicinal product for treatment of a CNS damage affecting neural stem cells, progenitor cells and/or cells derived from stem cells or progenitor cells.

2. Use according to claim 1, wherein said substance is growth hormone or a functionally equivalent analogue thereof.

3. Use according to claim 1, wherein said substance upon administration will increase the release of endogenous growth hormone.

4. Use according to any one of the claims 1-3, wherein said CNS damage affects the oligodendroglia, astroglia, and/or neuronal cells.

5. Use according to any one of the claims 1-4, wherein said CNS damage affects non-cholinergic neuronal cells, cholinergic neuronal cells, or glial cells.

6. Use according to any one of the claims 1-5, wherein said CNS damage is neural cell loss.

7. Use according to any one of the claims 1-6, wherein said CNS damage is caused by hypoxic injury, ischemic injury, and/or traumatic injury.

8. Use according to any one of the claims 1-7, wherein said medicinal product is formulated for intravenous infusion, intramuscular injection or subcutaneous injection.

9. Use according to any one of the claims 1-8, wherein said medicinal product is formulated so that the active substance will pass into the ventricles of the patient's brain when it is administered to a patient.

10. Use according to any one of the claims 1-9, wherein said medicinal product is formulated so that the

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active substance will pass into the cerebrospinal fluid of the patient when it is administered to a patient.

11. Use of a substance that upon administration to a patient will lead to a decreased concentration of growth hormone or a functionally equivalent analogue thereof for the production of a medicinal product for treatment of an abnormal condition affecting the central nervous system, wherein said abnormal condition is the consequence of axonal damage caused by concussion, axonal damage caused by head trauma, axonal damage caused by small vessel disease in the CNS, damage to the spinal cord after disease and/or trauma.

12. Use according to claim 11, wherein said substance is a negatively regulating growth hormone binding protein, a functionally equivalent analogous thereof, an antibody against growth hormone, a biologically active growth hormone receptor inhibitor, and/or an inhibitor of endogenous growth hormone release.

13. A method of propagating progenitor cells, stem cells and/or cells derived from said cells by administration of an effective amount of growth hormone or a functionally equivalent analogue thereof to stem cells, progenitor cells, neurons astroglial cells and/or oligodendrocytes in vitro.

14. A method of inducing lineage determination or inducing or maintaining the genesis of neurons, oligodendrocytes, astroglial cells from progenitor cells or stem cells in, or derived from, the central or peripheral nervous system in a patient, wherein a pharmaceutically effective amount of a substance that will lead to an increased concentration of growth hormone or a functionally equivalent analogue thereof is administered to said patient.

15. A method according to claim 14, wherein said substance is growth hormone or a functionally equivalent analogue thereof.

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16. A method according to claim 14, wherein said substance is a substance that increases the release of endogenous growth hormone.

17. A method according to claim 14, for treatment of an abnormal condition affecting the nervous system of a patient.

18. A method according to claim 17, wherein said condition affects the oligodendroglia, astroglia, and/or neuronal cells.

19. A method according to claim 17, wherein said condition affects the non-cholinergic neuronal cells, cholinergic neuronal cells, or glial cells.

20. A method according to claim 17, wherein said condition is a CNS damage or deficit.

21. A method according to claim 20, wherein said condition is neural cell loss.

22. A method according to claim 20, wherein said condition is memory loss.

23. A method according to claim 20, wherein said condition is caused by at least one factor selected from the group consisting of multiple sclerosis, hypoxic injury, ischemic injury, traumatic injury, Parkinson's disease, and demyelinating disorder.

24. A method according to claim 14, wherein said substance is administered by intravenous infusion, intramuscular injection or subcutaneous injection.

25. A method according to claim 14, wherein brain cells are removed from the patient after said administration, said brain cells then being propagated in vitro, followed by transplantation of the obtained cells back into the brains of the patient.

26. A method according to claim 25, wherein an effective amount of growth hormone or a functionally equivalent analogue thereof is administered to said brain cells during in vitro propagation.

27. A method of reducing the genesis of oligodendrocytes, neurons, astroglial cells from progenitor cells or

stem cells in, or derived from, the central or peripheral nervous system in a patient, wherein a pharmaceutically effective amount of a substance that will lead to a decreased concentration of growth hormone or a functionally equivalent analogue thereof is administered to said patient.

28. A method according to claim 27, wherein said substance is administration to the peripheral or central nervous system of said patient.

29. A method according to claim 27, wherein said substance is selected from the group consisting of negatively regulating growth hormone binding proteins, functionally equivalent analogous thereof, antibodies against growth hormone, biologically active growth hormone receptor inhibitors, and inhibitors of endogenous GH release.

30. A method according to claim 27, for treatment of a central nervous system injury.

31. A method according to claim 30, wherein said injury is the consequences of a factor selected from the group consisting of axonal damage caused by concussion, axonal damage caused by head trauma, axonal damage caused by small vessel disease in the CNS, damage to the spinal cord after disease or trauma.

AMENDED SHEET